



Early anticoagulation in patients with stroke and atrial fibrillation is associated with fewer ischaemic lesions at 1 month: the ATTUNE study

Angelos Sharobeam ¹, Longting Lin,² Christina Lam,¹ Carlos Garcia-Esperon ³, Yash Gawarikar,⁴ Ronak Patel,⁴ Matthew Lee-Archer,⁵ Andrew Wong,^{6,7} Michael Roizman,^{6,7} Amanda Gilligan,^{8,9} Andrew Lee,¹⁰ Kee Meng Tan,¹¹ Susan Day,¹² Christopher Levi,³ Stephen M Davis,¹ Mark Parsons,^{2,13} Bernard Yan¹

To cite: Sharobeam A, Lin L, Lam C, *et al.* Early anticoagulation in patients with stroke and atrial fibrillation is associated with fewer ischaemic lesions at 1 month: the ATTUNE study. *Stroke & Vascular Neurology* 2024;**9**: e002357. doi:10.1136/svn-2023-002357

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/svn-2023-002357>).

AS and LL contributed equally.

Received 1 February 2023

Accepted 5 May 2023

Published Online First

29 May 2023

ABSTRACT

Background The optimal time to commence anticoagulation in patients with atrial fibrillation (AF) after ischaemic stroke or transient ischaemic attack (TIA) is unclear, with guidelines differing in recommendations. A limitation of previous studies is the focus on clinically overt stroke, rather than radiologically obvious diffusion-weighted imaging ischaemic lesions. We aimed to quantify silent ischaemic lesions and haemorrhages on MRI at 1 month in patients commenced on early (<4 days) vs late (≥4 days) anticoagulation. We hypothesised that there would be fewer ischaemic lesions and more haemorrhages in the early anticoagulant group at 1-month MRI.

Methods A prospective multicentre, observational cohort study was performed at 11 Australian stroke centres. Clinical and MRI data were collected at baseline and follow-up, with blinded imaging assessment performed by two authors. Timing of commencement of anticoagulation was at the discretion of the treating stroke physician.

Results We recruited 276 patients of whom 208 met the eligibility criteria. The average age was 74.2 years (SD±10.63), and 79 (38%) patients were female. Median National Institute of Health Stroke Scale score was 5 (IQR 1–12). Median baseline ischaemic lesion volume was 5 mL (IQR 2–17). There were a greater number of new ischaemic lesions on follow-up MRI in patients commenced on anticoagulation ≥4 days after index event (17% vs 8%, p=0.04), but no difference in haemorrhage rates (22% vs 32%, p=0.10). Baseline ischaemic lesion volume of ≤5 mL was less likely to have a new haemorrhage at 1 month (p=0.02). There was no difference in haemorrhage rates in patients with an initial ischaemic lesion volume of >5 mL, regardless of anticoagulation timing.

Conclusion Commencing anticoagulation <4 days after stroke or TIA is associated with fewer ischaemic lesions at 1 month in AF patients. There is no increased rate of haemorrhage with early anticoagulation. These results suggest that early anticoagulation after mild-to-moderate acute ischaemic stroke associated with AF might be safe, but randomised controlled studies are needed to inform clinical practice.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Early anticoagulation after ischaemic stroke associated with atrial fibrillation (AF) may reduce the rate of recurrent diffusion-weighted imaging ischaemic lesions and increase the rate of new haemorrhage.
- ⇒ It is unknown whether early anticoagulation also reduces the rate of new silent ischaemic lesions.

WHAT THIS STUDY ADDS

- ⇒ Early anticoagulation (<4 days) after ischaemic stroke due to AF reduces the rate of new silent ischaemic lesions at 1 month without increasing the rate of new haemorrhage.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Early anticoagulation after mild-to-moderate acute ischaemic stroke due to AF might be safe, however, the results require further validation with randomised trials.

INTRODUCTION

Anticoagulant therapy decreases ischaemic stroke in patients with atrial fibrillation (AF) by 64% and decreases all-cause mortality by 24%.^{1,2} However, the optimal timing of anticoagulant commencement after acute ischaemic stroke remains uncertain. In patients with ischaemic stroke associated with AF, the risk of stroke recurrence within 14 days is 2-fold greater than patients without AF¹ and up to 1.3% per day.^{3,4} Delayed commencement of anticoagulant possibly increases the risk of recurrent stroke, while early initiation may increase haemorrhagic transformation.⁵ In addition, pivotal trials of direct oral anticoagulants (DOAC) excluded patients between 7 and 14 days,^{6–9} increasing the uncertainty regarding optimal timing of anticoagulation. On this basis, international guidelines vary in their recommendations on the timing of



© Author(s) (or their employer(s)) 2024. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Professor Bernard Yan;
Bernard.Yan@mh.org.au

anticoagulation commencement. European guidelines provide a weak recommendation for commencing anticoagulation 3–4 days after mild, small diameter (<1.5 cm) infarcts, 7 days for moderate infarcts and >14 days for large infarcts.¹⁰ UK guidelines recommend commencing anticoagulation after 14 days for disabling stroke but allow clinician discretion for milder strokes.¹¹ The American Heart Association (AHA) guidelines recommend commencement anywhere between 4 and 14 days for patients at low risk of haemorrhage and >14 days for high-risk patients.¹² There are also other guidelines, such as the 1-3-6-12 rule, which are used to guide clinical practice. This rule calls for a graded increase in anticoagulation commencement between 1 and 12 days, based on stroke severity.¹³

Although patients with AF have a high risk of clinically overt stroke, clinically silent ischaemic lesions form the vast majority of strokes in patients with AF. In a large study evaluating the relationship between MRI lesions and cognition in AF patients, 64% of ischaemic lesions were clinically silent.¹³ Silent ischaemic lesions are of clinical relevance, as they are associated with poor functional outcomes, poorer cognition and increased risk of dementia.^{14–17}

There is also evidence that asymptomatic poststroke haemorrhages are associated with clinically relevant outcomes. A recent meta-analysis analysing over 100 000 patients with poststroke haemorrhage, found that asymptomatic cerebral haemorrhage was associated with poorer 3-month functional outcomes. The majority of radiological haemorrhages were likewise associated with poorer 3-month functional outcomes, with the exception of grade 1 petechial haemorrhages.¹⁸

ATTUNE (ATrial fibrillation in sTroke-Utility of Neuroimaging Evaluation) was a prospective, multicentre study of clinical and radiological outcomes in patients commenced on early or late anticoagulation after ischaemic stroke or transient ischaemic attack (TIA).

Aims and hypothesis

ATTUNE aimed to quantify the rate of silent ischaemic lesions and haemorrhages on MRI at 1-month in patients commenced on early (<4 days ie, <96 hours) vs late (≥4 days) anticoagulation. We tested the hypothesis that early anticoagulation would result in fewer ischaemic lesions and more haemorrhages on 1-month follow-up MRI, compared with late anticoagulation.

Outcomes

The primary outcome was the proportion of patients with radiological evidence of recurrent ischaemic lesions on MRI, 1 month after ischaemic stroke or TIA, in patients commenced on early (<4 days) or late (≥4 days) anticoagulation. Secondary outcomes included: (1) the presence of intracerebral haemorrhage on follow-up MRI at 1 month and (2) the interaction between initial ischaemic lesion volume, new ischaemic lesions and new haemorrhages on the follow-up MRI.

The 4-day stratification was used as it is a common anticoagulation timepoint in European and American Heart Association/American Stroke Association guidelines. A 14-day cut-off was not used as in Australia the vast majority of patients are routinely anticoagulated prior to 14 days.

METHODS

Study design and setting

A multicentre, prospective observational cohort study was performed across 11 Australian metropolitan stroke centres in 5 different states. Patients were recruited over a 38-month period, between 15 May 2016 and 15 July 2019, with a final 3-month follow-up completed in October 2019.

Patients were stratified into two groups, early (<4 days after symptom onset) and late commencement (≥4 days after symptom onset). The timing of anticoagulation and agent used were at the discretion of the treating clinician.

Participants

Patients with a new or pre-existing diagnosis of non-valvular AF and clinical diagnosis of ischaemic stroke or TIA were eligible for inclusion. All patients were commenced on anticoagulation with a vitamin K antagonist (VKA) or DOAC <21 days after the index event. Patients in whom anticoagulation was contraindicated or not commenced within 21 days were excluded.

Baseline demographic characteristics, including age, sex, vascular risk factors, baseline National Institute of Health Stroke Scale (NIHSS) score, baseline and 3-month modified Rankin Score (mRS) score and acute reperfusion therapies delivered, were collected. Information about pre-existing anticoagulation and antithrombotic medication was also collected. Therapeutic anticoagulation was defined as either (1) an INR of ≥2.0 in patients on warfarin or (2) an oral anticoagulant dose appropriate to age and renal function in patients not on warfarin.

Imaging

Follow-up MRI was performed at baseline and 1 month on the same MR scanner in all included patients. Standard clinical sequences were performed and included diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC), susceptibility-weighted imaging and fluid attenuated inversion recovery, using a 1.5T or 3T MRI.

MRI analysis including baseline ischaemic lesion volume, new ischaemic lesions and new haemorrhages was performed at 1 month. Images were independently analysed by a stroke neurologist (AS) and a neuroradiologist (BY). Both raters were blinded to anticoagulant type, commencement time and each other's assessment. In case of disagreement, a third neuroimaging expert (MP) adjudicated.

An 'ischaemic lesion' was defined as a lesion which was both hyperintense on DWI and hypointense on ADC sequences. Patients without a DWI or ADC lesion on the initial MRI were determined to have a TIA.

Haemorrhagic transformation was classified according to the European Cooperative Acute Stroke Study criteria.¹⁹ Volumetric analysis of ischaemic lesions was performed using ITK-SNAP V.3.8.0.²⁰

Follow-up

Follow-up was performed at 1 month and 3 months via telephone or in person, to collect imaging data and assess functional status. If patients developed new acute neurological symptoms felt secondary to a new stroke, further neuroimaging was obtained.

Statistical analysis

We calculated a sample size of 97 patients receiving oral anticoagulation ≥ 4 days and 97 patients receiving anticoagulation < 4 days would yield an alpha of 0.05 and beta of 0.02 with 80% power to detect a difference in new ischaemic lesions between the two groups. This was based on an expected event rate (new ischaemic lesions on MRI) for the first group (late anticoagulation) of 25% and for the second group (early anticoagulation) of 10%.²¹

Continuous data were analysed and compared using a two-sample t-test and reported as means with SD. Nominal data were analysed and compared by using a χ^2 test and reported as percentages. Non-parametric tests were used to analyse ordinal and non-Gaussian data and reported as medians with IQRs. The Shapiro-Wilks test was used to determine normality. Primary and secondary outcome measures were reported as ORs with 95% CIs. The effect of confounding variables was ascertained using multivariate logistic regression analysis. Multiple logistic regression analysis was used to study the association between baseline ischaemic lesion volume, treatment group (early vs late), new ischaemic lesions and haemorrhages. Sensitivity analyses were also performed to determine the effect of different anticoagulant commencement times on new ischaemic and haemorrhagic lesions. A $p < 0.05$ was used to

determine statistical significance. For variables in which data were missing for $> 5\%$ of cases, a multiple imputation analysis was performed. All statistical analyses were performed by using SPSS V.27.²²

Data management and ethics

Clinical and imaging data collected at each participating site were uploaded to a web-based registry. All imaging data were automatically deidentified on upload via the provision of a unique identifier. No identifying clinical data were entered.

This manuscript adheres to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.²³

RESULTS

Participants

Two hundred and seventy-six patients were recruited into the study. Of these, 68 patients were excluded. Ten patients did not have anticoagulation data available. Forty-nine patients did not have repeat MRI images available for analysis. A further nine patients had anticoagulation commenced ≥ 21 days after symptom onset. A total of 208 patients were subsequently analysed (figure 1). There were 107 patients who received anticoagulation < 4 days (early anticoagulation) and 101 who received anticoagulation ≥ 4 days (late anticoagulation) after the index event.

The mean age of included patients was 74.2 (SD ± 10.6) and 79 (38%) patients were female. The median NIHSS score was 5 (IQR 1–12) and median baseline ischaemic lesion volume on DWI was 5 mL (IQR 2–17) reflecting a predominantly mild to moderate stroke severity cohort.

Most baseline demographic variables did not differ significantly between included and excluded patients, except for hypertension which was more common in included patients (table 1). Excluded patients

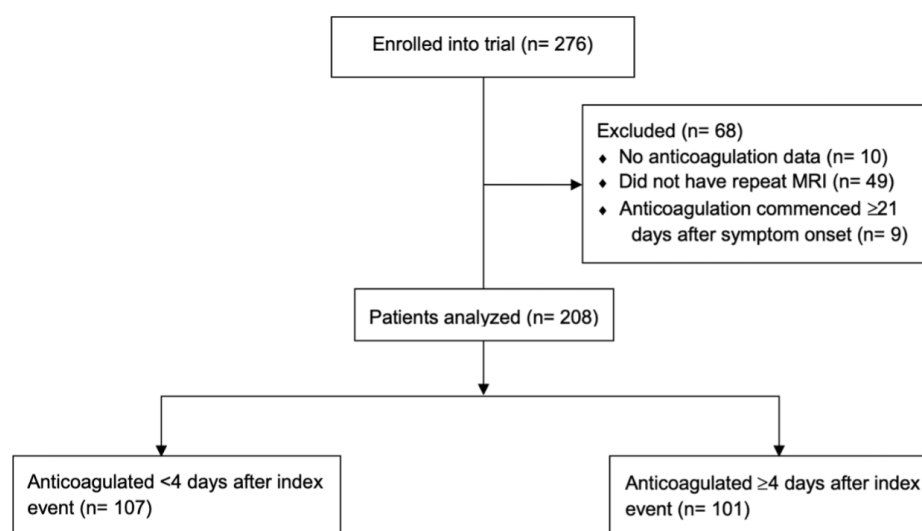


Figure 1 Patient selection flow chart. Exclusions included lack of anticoagulation data, no follow-up MRI and anticoagulation commencement ≥ 21 days after symptom onset.

Table 1 Baseline variables in included and excluded patients

Variable	Excluded patients	Included patients	P value
	68	208	–
Age (mean±SD)	74.3±12.1	74.2±10.6	0.95
Sex (female)	38% (26)	38% (79)	0.93
Hypertension	51% (35)	64% (134)	0.05
Previous stroke	12% (8)	12% (25)	0.97
Previous TIA	6% (4)	9% (19)	0.40
Diabetes mellitus	16% (11)	19% (39)	0.64
Congestive cardiac failure	9% (6)	9% (19)	0.94
Ischaemic heart disease	15% (10)	20% (41)	0.43
Pre-existing AF	78% (53)	80% (167)	0.89
Therapeutic anticoagulation prior to admission	13% (7)	16% (26)	0.65
Thrombolysis	9% (6)	17% (35)	0.11
Endovascular thrombectomy	9% (6)	13% (27)	0.25
Median initial ischaemic lesion volume (IQR)	13 (3.8–29.3)	5 (2–17.3)	0.33
TIA	9% (6)	6% (12)	0.29
Median admission NIHSS score (IQR)	3 (0–9)	5 (1–12)	0.34
Median premorbid mRS score (IQR)	0 (0–0)	0 (0–0)	0.76

AF, atrial fibrillation; mRS, modified Rankin Score; NIHSS, National Institute of Health Stroke Scale; TIA, transient ischaemic attack.

compared with included patients tended to have larger ischaemic lesion volumes but this did not reach statistical significance (median 13 mL (IQR 3–29) vs 5 mL (IQR 2–18), $p=0.33$).

Demographic variables were largely similar between early and late anticoagulation groups (table 2). There was a higher median initial ischaemic lesion volume in the late anticoagulation group, compared with early

Table 2 Baseline variables in early and late anticoagulation groups

Variable	Early anticoagulation	Late anticoagulation	P value
N	107	101	–
Age (mean±SD)	74.2±10.7	74.3±10.5	0.40
Sex (female)	38% (41)	38% (38)	0.96
Hypertension	65% (70)	63% (64)	0.84
Previous stroke	13% (14)	11% (11)	0.73
Previous TIA	8% (8)	11% (11)	0.38
Diabetes mellitus	16% (17)	22% (22)	0.23
Congestive cardiac failure	8% (9)	10% (10)	0.64
Ischaemic heart disease	21% (22)	19% (19)	0.84
Pre-existing AF	82% (88)	78% (79)	0.65
Therapeutic anticoagulation prior to admission	22% (19)	9% (7)	0.02
Thrombolysis	16% (17)	18% (18)	0.64
Endovascular thrombectomy	15% (16)	11% (11)	0.64
TIA	7% (7)	5% (5)	0.62
Median initial ischaemic lesion volume (mL) (IQR)	3.5 (1–10)	11 (3–26.5)	0.001
Median admission NIHSS score (IQR)	4 (1–8.5)	6 (2–13.5)	0.12
Median premorbid mRS score (IQR)	0 (0–0)	0 (0–0)	0.11

AF, atrial fibrillation; mRS, modified Rankin Score; NIHSS, National Institute of Health Stroke Scale; TIA, transient ischaemic attack.

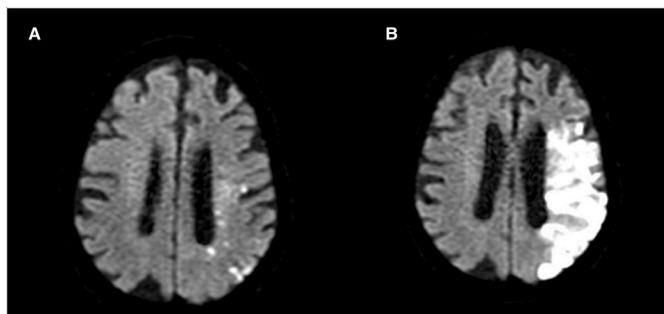


Figure 2 Example of a patient with scattered left MCA territory ischaemic lesions on baseline DWI (A) and a new left MCA territory ischaemic lesion at 1 month (B). DWI, diffusion-weighted imaging.

(11 mL (IQR 3–26), vs 3.5 mL (IQR 1–10), respectively, $p=0.001$). Patients in the late group were less likely to be on therapeutic anticoagulation prior to admission when compared with the early group (9% vs 22%, respectively, $p=0.02$).

Prior antiplatelet usage was similar between the two groups (online supplemental table 1). There was no significant difference in median onset-to-MRI times in the early group, compared with the late group (median 28 hours (IQR 21–48) vs a median of 44 hours (IQR 22–82), respectively, $p=0.13$).

Across the study cohort of 211 patients, 6 patients (3%) were commenced on a VKA after enrolment, and 205 patients (97%) on a DOAC. Of the patients commenced on a VKA, three were in the late group and three in the early group. Given the very low numbers, further analysis of outcomes between patients commenced on a VKA versus DOAC was not performed.

Three patients represented with new stroke symptoms within 3 months. One patient had a TIA, one had an ischaemic stroke and one had an intracerebral haemorrhage. All these events occurred in the late anticoagulation group.

Outcomes

A total of 27 patients (13%) had new ischaemic lesions on follow-up MRI (figure 2A,B). Nine out of 107 (8%) patients in the early group had a new ischaemic lesion compared with 18/101 (17%) patients in the late group ($p=0.04$). When TIA patients were excluded, 8/100 (8%) patients in the early group had a new ischaemic lesion compared with 17/96 (18%) in the late group ($p=0.04$).

A total of 55 patients (26%) had new haemorrhages on follow-up MRI (figure 3A,B). Twenty-three out of 107 (22%) patients in the early group had a new haemorrhage. Thirty-two out of 101 (32%) patients in the late group had a new haemorrhage. There was no statistically significant difference in the incidence of new haemorrhage between the two groups ($p=0.10$). Only one patient had a symptomatic haemorrhage—a grade 2 parenchymal haemorrhage (PH2) in the late anticoagulation group, which extended outside the region of ischaemia. Twenty-four patients had a grade 1 petechial haemorrhage (HI1),

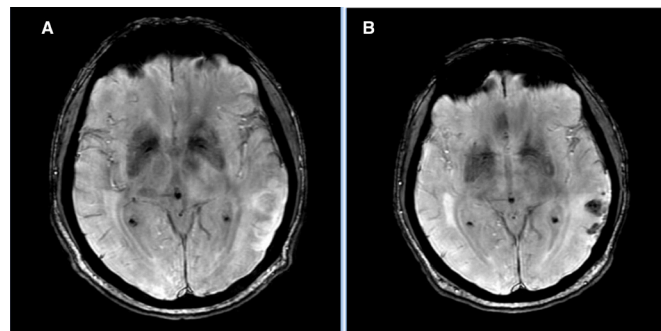


Figure 3 Example of a patient with no haemorrhage on baseline SWI (A) and new haemorrhagic transformation at 1 month (B). SWI, susceptibility-weighted imaging.

13 had a grade 2 petechial haemorrhage (HI2) and 3 patients had a grade 1 parenchymal haemorrhage (PH1), all within the region of ischaemia. Eighteen patients had a remote haemorrhage.

A multivariate regression analysis was performed to determine the effect of confounding variables on the primary and secondary outcomes. Baseline ischaemic lesion volume was the only variable to significantly differ between the two groups (table 2) and was entered into the model. After adjusting for baseline volume, the timing of anticoagulation commencement remained independently predictive of new ischaemic lesions at 1 month (aOR 2.41, (95% CI 1.0 to 5.83), $p=0.045$).

There was also an interaction between anticoagulation timing and baseline ischaemic lesion volume in predicting new haemorrhages (OR 1.02 (95% CI 1.00 to 1.04), $p=0.002$). For the early anticoagulation group, increased baseline ischaemic lesion volume was associated with a higher rate of new haemorrhage. However, for the late anticoagulation group, the new haemorrhage rate was not associated with baseline ischaemic lesion volume.

Baseline ischaemic lesion volume was then dichotomised by the median value of 5 mL (≤ 5 mL and > 5 mL). In patients with a baseline ischaemic lesion volume of > 5 mL, there was no significant difference in the rate of new haemorrhage between early and late anticoagulation groups (41% vs 36%, respectively, $p=0.58$). However, in patients with a baseline ischaemic lesion volume ≤ 5 mL, the rate of new haemorrhages was lower in the early compared with late anticoagulation group (6% vs 10%, respectively, $p=0.02$) (figure 4).

There was no interaction between anticoagulation timing and baseline ischaemic lesion volume in predicting new ischaemic lesions (OR 1.00 (95% CI 0.98 to 1.02), $p=0.75$). For patients with a volume > 5 mL, the rate of new ischaemic lesions were lower in the early (5%) compared with the late anticoagulation group (15%). For patients with a volume ≤ 5 mL, the rate of new ischaemic lesions were also lower in the early (10%) compared with the late (23%) anticoagulation group.

A total of 178/208 patients had 3-month follow-up data available. A multiple imputation analysis was, therefore,

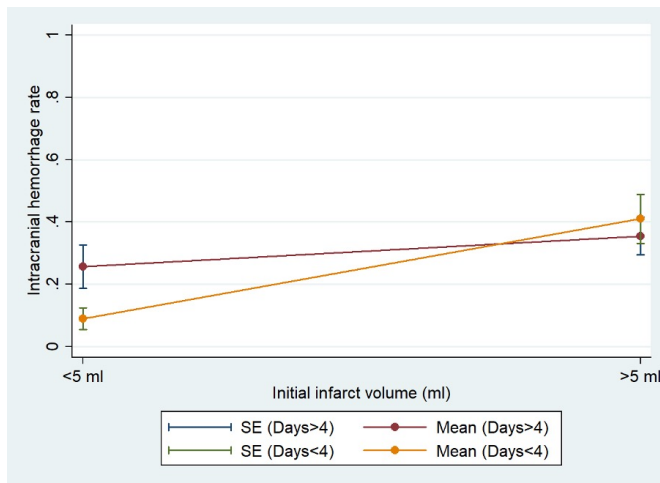


Figure 4 Interaction of baseline ischaemic lesion volume and treatment time in predicting new haemorrhage rate at 1 month. There was a significant interaction seen in the early, but not late, anticoagulation group.

performed to account for missing variables. There was no significant difference in poor 3-month functional outcomes (mRS 3–6) between the early (31%) and late groups (36%) ($p=0.56$). Median ischaemic lesion volume also did not differ between patients with good (median 6, IQR 1–18) or poor functional outcomes (median 5, IQR 2–16), $p=1.0$.

Sensitivity analysis

Further analysis was performed to determine the association of different anticoagulation start times on new lesion rates (figure 5). Patients were stratified into four different time points—anticoagulation commencement within 1 day, between 2 and 3 days, 4 and 6 days and 7 days or later. Increasing treatment delay was predictive of

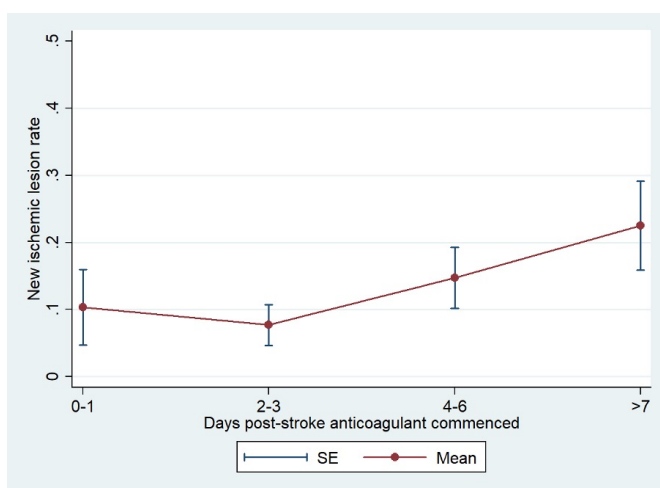


Figure 5 Time points for anticoagulation commencement and new ischaemic lesion rate. Patients in time point 1 had anticoagulation commenced within 1 day, patients in time point time between 2 and 3 days, patients in time point 3 between 4 and 6 days and patients in time point 4, 7 days or later.

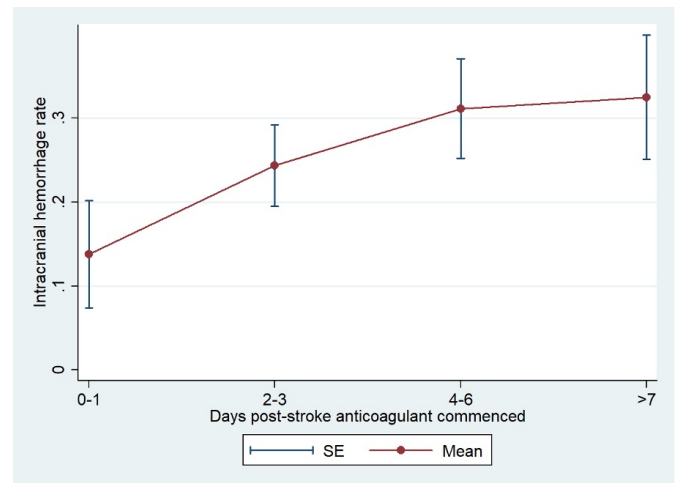


Figure 6 Association between anticoagulation commencement time and new haemorrhage rate at 1 month. There was a higher risk of new haemorrhage observed with later anticoagulation commencement.

new ischaemic lesions (OR 1.57 (95% CI 1.01 to 2.43), $p=0.04$).

A sensitivity analysis was also performed to determine the association of different anticoagulation start times on haemorrhage, with the same time points used above (figure 6). There was a trend towards higher rates of new haemorrhages with later anticoagulation commencement, but this was not statistically significant (OR 1.37 (95% CI 0.98 to 1.90), $p=0.06$).

DISCUSSION

In this mild-to-moderate stroke severity cohort, there was a twofold increase in new radiological ischaemic lesions in AF patients commenced on late versus early anticoagulation, following an ischaemic event (17% vs 8%, $p=0.04$). Our results also suggest that initial ischaemic lesion volume is a factor which influences the rate of new haemorrhage. However, early anticoagulation did not increase the number of new haemorrhages compared with late anticoagulation with ischaemic lesion volumes of >5 mL ($p=0.58$). Indeed, there was a lower number of haemorrhages in the early initiation group with smaller ischaemic lesion volumes of ≤ 5 mL. To the best of our knowledge, our study is the first to report these associations between a specific ischaemic lesion volume, anticoagulation timing and new haemorrhages. The ATTUNE study is also the first to show an association between commencing anticoagulation <4 days after an ischaemic event and fewer silent ischaemic lesions at 1 month.

Previous studies have demonstrated that the prevalence of silent ischaemic lesion rates in patients with AF are as high as 40%.^{13 24} The triple AXEL study²⁵ examined ultraearly initiation of anticoagulation in patients anticoagulated with rivaroxaban or warfarin after stroke. The incidence of new ischaemic lesions at 1 month was 30% in the rivaroxaban group and 36% in the warfarin group. In

the Swiss-AF study,¹³ most patients were already on anti-coagulation, which may, therefore, have underestimated the true silent ischaemic lesion rate. The 13% new ischaemic lesion rate seen in our study is lower than the triple AXEL study, which may in part be reflective of the use of different anticoagulant agents (warfarin or rivaroxaban in triple AXEL).

The risk of recurrent haemorrhage has traditionally been thought to increase with larger baseline ischaemic lesion volumes.^{5 26} In the mild-to-moderate severity subgroup of patients, however, our results do not support delaying anticoagulation in patients with AF following an ischaemic event to potentially reduce haemorrhage risk. Early anticoagulation also has the practical advantage of initiation during the inpatient stay after stroke, which may lead to greater anticoagulation uptake, as well as potentially earlier hospital discharge.⁴

Several randomised clinical trials are attempting to determine the optimum start time of anticoagulation in AF-associated stroke—ELAN,²⁷ OPTIMAS,²⁸ TIMING²⁹ and START.³⁰ These studies will collectively enrol over 9000 patients and provide further evidence to support anticoagulant timing decisions. The recently published TIMING trial found that early initiation (≤ 4 days) of anti-coagulant therapy was non-inferior to later (5–10 days) commencement for the primary composite outcome of recurrent ischaemic stroke, symptomatic ICH and all-cause mortality at 90 days.²⁹

Our focus on imaging in this study also gives a more accurate reflection of the true ischaemic lesion rate as opposed to clinical events alone. Given the association with recurrent stroke, cognitive impairment and potentially poorer functional outcomes,^{14–16} silent ischaemic lesion rates are an important diagnostic tool which have the potential to be used as a future stroke risk stratification tool, when combined with other risk factors.

Limitations

Our study has a few limitations. First, 49 patients did not have follow-up MRI imaging available and were excluded, which may be a source of bias and reduce statistical power. In many of these patients, the reasons for this could not be ascertained. Potential reasons include non-attendance due to death, recurrent hospitalisation or stroke, moderate or severe disability (mRS 4–5) or discharge to a regional or rehabilitation centre after admission. The study was performed at stroke centres which see a higher proportion of stroke patients. ATTUNE enrolled a mild-to-moderate stroke severity cohort and was an observational study, leaving open the possibility of further selection bias and confounding. The timing of initiation of anticoagulation was at the discretion of the treating clinician or local protocol. The cut-off between early versus late anticoagulation (4 days) was based on pre-existing literature and guidelines, as a reasonable delineation. However, we acknowledge there is wide variability in clinical practice. The small cohort size limits the ability to statistically adjust for these limitations, and in particular

factors, measured and unmeasured, associated with the decision to give early anticoagulation.

Strengths

The use of MRI in ATTUNE in both early and late imaging allowed more sensitive diagnosis of the true early ischaemic lesion and haemorrhage rates after commencing anticoagulation. Additional strengths of our study, include its prospective nature and being performed at multiple large stroke centres. Baseline characteristics were also similar between groups, which improves the internal validity of the study. Our study is more reflective of real-world scenarios and practice, compared with randomised trials, with no exclusions based on age, presenting NIHSS, functional status or comorbidities.

CONCLUSION

The results of this study add to pre-existing evidence in the field regarding the optimal time to commence anticoagulation after mild-to-moderate acute ischaemic stroke. Silent ischaemic lesions and ischaemic lesion volume are both important markers which can guide decision-making. The results of ATTUNE cannot yet inform clinical practice but may be exploratory and hypothesis generating for future studies. We await the results of further randomised trials which will provide further, complementary evidence to guide decision-making.

Author affiliations

¹Melbourne Brain Centre at Royal Melbourne Hospital, Parkville, Victoria, Australia

²University of New South Wales South Western Sydney Clinical School, Liverpool, New South Wales, Australia

³Department of Neurology, John Hunter Hospital, Newcastle, New South Wales, Australia

⁴Department of Neurology, Calvary Public Hospital, Canberra, Australian Capital Territory, Australia

⁵Department of Neurology, Northern Hospital Epping, Epping, Victoria, Australia

⁶Department of Neurology, Royal Brisbane and Women's Hospital, Herston, Queensland, Australia

⁷The University of Queensland School of Medicine, Herston, Queensland, Australia

⁸Neurosciences Clinical Institute, Epworth Healthcare, Richmond, Virginia, Australia

⁹Department of Neurology, Austin Health, University of Melbourne, Heidelberg, Victoria, Australia

¹⁰Flinders University College of Medicine and Public Health, Adelaide, South Australia, Australia

¹¹Department of Neurology, Gold Coast University Hospital, Southport, Queensland, Australia

¹²The University of Sydney Northern Clinical School, St Leonards, New South Wales, Australia

¹³Department of Neurology and Neurophysiology, Liverpool Hospital, Liverpool, New South Wales, Australia

Twitter Angelos Sharobeam @asharobeam

Contributors AS and LL contributed equally as first authors and were responsible for drafting and editing the manuscript. AS collated the data and LL performed the statistical analysis. AS, BY and MP performed blinded image analyses. MP and BY conceptualised the project. CLam, CG-E, YG, RP, LL, AL, MR, KMT, AG, AL and SD were involved in data collection. AS is the guarantor and accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish. All authors provided critical input into the manuscript and approved the final version.

Funding This study was supported by funding from Bayer Pharmaceuticals.

Disclaimer Bayer had no role in the study design, data collection, data analysis, manuscript preparation or the decision to publish.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Royal Melbourne Hospital Human Research Ethics Committee Reference Number: HREC 2016.140. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Study data are available on reasonable request to the corresponding author.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Angelos Sharobeam <http://orcid.org/0000-0001-5833-7632>

Carlos Garcia-Esperon <http://orcid.org/0000-0001-8843-5890>

REFERENCES

- Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;146:857–67.
- Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;383:955–62.
- Seiffge DJ, Werring DJ, Paciaroni M, et al. Timing of anticoagulation after recent ischemic stroke in patients with atrial fibrillation. *Lancet Neurol* 2019;18:117–26.
- Paciaroni M, Agnelli G, Micheli S, et al. Efficacy and safety of anticoagulant treatment in acute Cardioembolic stroke: a meta-analysis of randomized controlled trials. *Stroke* 2007;38:423–30.
- Butcher KS, Ng K, Sheridan P, et al. Dabigatran treatment of acute Noncardioembolic ischemic stroke. *Stroke* 2020;51:1190–8.
- Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369:2093–104.
- Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139–51.
- Connolly SJ, Ezekowitz MD, Yusuf S, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139–51.
- Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in Nonvalvular atrial fibrillation: a European stroke organization guideline. *Eur Stroke J* 2019;4:198–223.
- Klijn CJ, Paciaroni M, Berge E, et al. Antithrombotic treatment for secondary prevention of stroke and other thromboembolic events in patients with stroke or transient ischemic attack and non-valvular atrial fibrillation: a European stroke organization guideline. *Eur Stroke J* 2019;4:198–223.
- Intercollegiate Stroke Working Party. National clinical guideline for stroke. 2016. Available: <https://www.rcplondon.ac.uk/guidelines-policy/stroke-guidelines> [Accessed 31 Jan 2022].
- Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American heart Association/American stroke Association. *Stroke* 2019;50:e344–418.
- Kirchhof P, Benussi S, Kotecha D, et al. ESC scientific document group. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;37:2893–962.
- Conen D, Rodondi N, Müller A, et al. Relationships of overt and silent brain lesions with cognitive function in patients with atrial fibrillation. *J Am Coll Cardiol* 2019;73:989–99.
- Qu JF, Chen YK, Zhong HH, et al. Preexisting cerebral abnormalities and functional outcomes after acute ischemic stroke. *J Geriatr Psychiatry Neurol* 2019;32:327–35.
- Kühne M, Krisai P, Coslovsky M, et al. Silent brain ischemic lesions impact on cognitive function in atrial fibrillation. *Eur Heart J* 2022;43:2127–35.
- Vermeer SE, Prins ND, den Heijer T, et al. Silent brain ischemic lesions and the risk of dementia and cognitive decline. *N Engl J Med* 2003;348:1215–22.
- He J, Fu F, Zhang W, et al. Prognostic significance of the clinical and radiological Haemorrhagic transformation subtypes in acute ischaemic stroke: a systematic review and meta-analysis. *Eur J Neurol* 2022;29:3449–59.
- Hacke W, Kaste M, Fieschi C, et al. Intravenous Thrombolysis with recombinant tissue plasminogen activator for acute Hemispheric stroke. *JAMA* 1995;274:1017.
- Yushkevich PA, Piven J, Hazlett HC, et al. User-guided 3D active contour Segmentation of anatomical structures: significantly improved efficiency and reliability. *Neuroimage* 2006;31:1116–28.
- Nomura E, Ohshita T, Imamura E, et al. Early administration of non-vitamin K antagonist oral anticoagulants for acute ischemic stroke patients with atrial fibrillation in comparison with warfarin mostly combined with heparin. *Circ J* 2015;79:862–6.
- IBM. SPSS Statistics for Windows, version 27. Armonk, N.Y, USA: IBM Corp,
- Elm E von, Altman DG, Egger M, et al. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007;335:806–8.
- Kalantarian S, Ay H, Gollub RL, et al. Association between atrial fibrillation and silent cerebral infarcts: a systematic review and meta-analysis. *Ann Intern Med* 2014;161:650–8.
- Hong KS, Kwon SU, Lee SH, et al. Phase 2 exploratory clinical study to assess the effects of Xarelto (Rivaroxaban) versus warfarin on ischemia, bleeding, and hospital stay in acute cerebral infarcts in patients with non-valvular atrial fibrillation (Triple AXEL) study group. Rivaroxaban vs warfarin sodium in the ultra-early period after atrial fibrillation-related mild ischemic stroke: a randomized clinical trial. *JAMA Neurol* 2017;74:1206–15.
- Paciaroni M, Agnelli G, Corea F, et al. Early hemorrhagic transformation of brain infarct: rate, predictive factors, and influence on clinical outcome: results of a prospective multicenter study. *Stroke* 2008;39:2249–56.
- Early versus late initiation of direct oral anticoagulants in post-ischemic stroke patients with atrial fibrillation (ELAN): an international, multicentre, randomized-controlled, two-arm, assessor-blinded trial (ELAN). Clinicaltrials.Gov. 2022. Available: <https://www.clinicaltrials.gov/ct2/show/NCT03148457> [Accessed 22 Feb 2022].
- OPTIMAS: optimal timing of anticoagulation after acute ischemic stroke: a randomized controlled trial (OPTIMAS). Clinicaltrials.Gov. 2022. Available: <https://www.clinicaltrials.gov/ct2/show/NCT03759938> [Accessed 22 Feb 2022].
- TIMING of oral anticoagulant therapy in acute ischemic stroke with atrial fibrillation. Clinicaltrials.Gov. 2022. Available: <https://www.clinicaltrials.gov/ct2/show/NCT02961348> [Accessed 22 Feb 2022].
- Optimal delay time to initiate anticoagulation after ischemic stroke in atrial fibrillation (START). Clinicaltrials.Gov. 2022. Available: <https://www.clinicaltrials.gov/ct2/show/NCT03021928> [Accessed 22 Feb 2022].